REMARKS

Claim 19 is the only pending claim for examination. Claim 19 is not amended herewith. No new matter has been added.

Double Patenting Rejection

Claim 19 was provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-11 and 13-30 of copending application No. 09/818918. The rejection is a provisional one since none of the claims in the 09/818918 application has been found allowable. Applicants defer substantive rebuttal until the above-identified claims are allowed.

Rejections under 35 U.S.C. §112

The Examiner rejected claim 19 under 35 U.S.C. §112 for lack of enablement commensurate in scope with the claimed invention.

The Examiner has maintained the rejection of the claims of record under 35 U.S.C. §112. Pages 3-11 of the Office Action dated June 2, 2006 repeat the rejection found in the Office Action dated October 7, 2005 with the exception that the rejection based on one of the papers that was cited in support of the lack of enablement rejection has been dropped. Applicants thank the Examiner for the acknowledgment that the rejection based on unpredictability supported by such reference has been withdrawn. Pages 11-13 of the Office Action address the Examiner's reasons for maintaining the rejection for lack of enablement. Each of these issues is addressed herein. The reasons for maintaining the rejection are addressed first.

Response to the Examiner's reasons for maintaining the rejection:

1. Discussion of References cited in support of lack of enablement

Initially Applicants thank the Examiner for the acknowledgement that McCluskie et al is not relevant to the enablement of the pending claims.

The Examiner has cited Krieg et al 2000, Wohlleben et al 2001, Kline et al 2002, Kline et al 1998, Weiner et al 2000, Agrawal et al 2000, Satoh et al 2002, Dziadzio et al 2004, and

Metzger et al 1999 for the proposition that the state of the art is unpredictable with respect to the effectiveness of the claimed method. In response, Applicants provided a detailed explanation for as to why each of the references does not support a lack of enablement of the claim. The Examiner responded that "even though these references may suggest the possibility of CpG's usefulness, they still also indicate even several years after Applicants' effective filing date that the scope of the claimed composition is not enabled." (page 12.) This is a mischaracterization of Applicants arguments. In the previous communication, Applicants rebutted the argument for each of the cited references, demonstrating that the teachings cited for lack of enablement were irrelevant, taken out of context or missing altogether. In the instances where it was applicable, Applicants also pointed out where the references were consistent with the teachings of the instant invention. This, however, did not form the basis of Applicants arguments. The Examiner is respectfully requested to respond to every aspect of the rebuttal. Each is re-iterated below for the record. Applicants also wish to point out that the claim is directed to a method not a composition.

The Examiner has pointed to two previously un-cited passages from Weiner et al. in support of maintenance of the rejection. The first statement is:

> "Weiner cautions that despite therapeutic promise of some CpG ODNs, all CpG ODNs are not alike and more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset or CpG ODN sequence."

In addition to the arguments reiterated below, Applicants wish to point out that the sentence paraphrased by the Examiner is simply an opinion by Dr. Weiner stating that more research should be performed to better understand these drugs. This sentence is not sufficient to demonstrate any unpredictability or lack of enablement. Further research needs to be performed on many FDA approved drugs. Biotechnology research is continually evolving. The law does not require, for a claim to be enabled, that further research to elucidate mechanisms of action, clinical preferences etc not be performed. Additionally the sentence is too general to support the lack of enablement of the claim. The Weiner reference is a review article summarizing in vitro and in vivo work as well as the use of CpG to promote innate immunity, as an immune adjuvant, for the treatment of infectious disease, allergy, asthma, and cancer. It is unclear whether the broad statement is applicable to all of these indications.

Finally, the statement must be read in context. It is found within the conclusion paragraph on page 461. Another sentence in the same paragraph states:

> "Recognition of the potent immunostimulatory effects of CpG ODN suggest that such agents may be important agents in the basic immunology laboratory, and in the treatment and prevention of a broad range of diseases."

On balance, the conclusion found in the paragraph cited by the Examiner is not inconsistent and does not support a finding of lack of enablement of the claimed invention.

The second teaching from Weiner cited by the Examiner is:

> "Weiner teaches that the clinical effects of CpG ODN have not yet been explored and further work with the immunostimulatory nucleic acids in both the laboratory and the clinic are needed before their true promise as investigational immunological and therapeutic agents is known."

Initially, Applicants wish to point out that clinical data is not necessary for enablement of a claimed invention. Human testing, which is the domain of the FDA and not the USPTO, is beyond the enablement standard required for, and thus should not be a bar, to patentability. In re Brana, 51 F.3d 1560 (Fed. Cir. 1995).

Additionally, Weiner is a post-filing date reference. Although Weiner states that the clinical effects of CpG ODN have not been explored, several other post-filing date references are in direct contrast to this. For instance, several clinical Phase I and II studies have been performed in human subjects. (See for example Creticos et al, Immunotherapy with immunostimulatory oligonucleotides linked to purified ragweed Amb a 1 allergen: effects on antibody production, nasal allergen provocation, and ragweed seasonal rhinitis, J Allergy Clin. Immunol. 109(4), 742-743. 2002; Simons et al, Selective immune redirection in humans with ragweed allergy by injecting Amb a 1 linked to immunostimulatory DNA, J Allergy Clin Immunol 113, 1144-1151 (2004); Krieg et al, Induction of systemic Th1-like innate immunity in normal volunteers following subcutaneous but not intravenous administration of CPG 7909, a synthetic B-class CpG oligodeoxynucleotide TLR9 agonist, J Immunother. 27, 460-471 (2004); Cooper et al, CpG 7909, an immunostimulatory TLR9 agonist oligodeoxynucleotide, as adjuvant to Engerix-B HBV vaccine in healthy adults: A double-blind Phase I/II study, J Clin. Immunol 24, 693-702 (2004); Halperin et al, A phase I study of the safety and immunogenicity of recombinant hepatitis B surface antigen co-administered with an immunostimulatory

phosphorothioate oligonucleotide adjuvant, Vaccine 21, 2461-2467 (2003); Siegrist et al, Co-administration of CpG oligonucleotides enhances the late affinity maturation process of human anti-hepatitis B vaccine response, Vaccine 23, 615-622 (2004); Cooper et al, Safety and Immunogenicity of CpG 7909 Injection as an Adjuvant to Fluarix Influenza Vaccine, Vaccine 22, 3136-3143 (2004); Speiser et al, Rapid and strong human CD8(+) T cell responses to vaccination with peptide, IFA, and CpG oligodeoxynucleotide 7909, J Clin. Invest 115, 739-746 (2005); van Ojik et al, Phase I/II study with CpG 7909 as adjuvant to vaccination with MAGA-3 protein in patients with MAGE-3 positive tumors, Ann.Oncol.13, 157. 2003., copies attached to IDS)

The Examiner further cited Leung, 1999, to demonstrate that "the long-term benefits of treatment with CpG ODN remain speculative." Applicants have reviewed the reference in its entirety and cannot find a basis for the rejection. Applicants could not identify any teaching related to CpG oligonucleotides. In the prior Office Action, the Examiner stated that "chronic AD skin has significantly fewer IL-4 and IL-13 mRNA-expressing cells but higher numbers of IL-5, GM-CSF, IL-12 and IFN-γ mRNA expression than has acute AD skin" It is unclear what relevance this has for the claimed invention. The Examiner is respectfully requested to provide more detail so that Applicants can address such rejection.

2. Discussion of data

The Examiner has acknowledged on pages 12-13 that some CpG ODN are capable of stimulating a Th1 immune response. In support of maintaining the rejection in view of inadequate support in the specification, the Examiner then poses 2 questions. No arguments or evidence is presented. The Examiner has not provided a successful rebuttal of Applicants arguments in response to the original rejection. Thus it is specifically requested that the rejection be withdrawn. Nevertheless, Applicants address each of the specific questions below.

The Examiner asks "is inducing an immune response indicative of treating an allergic response to a antigen or allergy related disorder?" The relevance of this question is not understood. Applicants have not argued that any compound that induces an immune response will be useful for treating allergy. To the contrary Applicants have argued that a class of molecules having a common structural motif promote the development of an immune response that is Th1 biased and when administered in vivo reduce eosinophil accumulation and promote

an environment that is useful for treating allergy. Numerous CpG ODNs were tested and the data is described in the specification. No evidence has been presented by the Examiner to suggest that one of skill in the art would not accept Applicants conclusion that CpG ODNs are useful for treating allergy based on the data and description presented in the specification. In the absence of such evidence, the rejection should be withdrawn.

The Examiner also states "further there are numerous antigens that induce a Th1 biases immune response, is one skilled in the art to assume that each of these antigens is sufficient to treat an allergic response or allergy related disorder." (sic)

Initially, the Examiner is requested to identify scientific support or evidence for her statement that "numerous antigens" "induce a Th1 biased immune response". Applicant is not aware of numerous antigens that produce a Th1 biased immune response. Purified antigens typically induce no immune response at all. In the case of allergy, which is most relevant to the current claim set, the allergens most commonly have unusual structures, such as pollen grains with highly repeating structures, exposure to which results in a Th2 response. As far as applicant is aware most antigens do not produce a Th1 biased response unless the antigen exposure is in the context of an infectious agent, or delivery of a Th1-inducing drug, such as the CpG ODN of the present invention. Additionally, applicants have not presented arguments that anything that produces a Th1 biased immune response will necessarily be useful for treating allergy. Applicants have presented numerous data in the specification to identify a pattern of immune response that is useful for treating allergy. Th1 is an example.

Applicants have presented data and asserted that it correlates with the scope of the claimed invention. The Examiner has not presented any objective evidence to demonstrate why it does not correlate. The rejection should be withdrawn.

Rejections repeated from prior office action but not addressed:

As discussed above, the Examiner re-iterated most of the rejections under 35 USC 112 presented in the prior Office Action dated October 7, 2005. Other than the specific points discussed above, the Examiner has not addressed any of Applicants' arguments filed in response to the Office Action dated October 7, 2005. Thus, Applicants present arguments to address each of these rejections again. It is specifically requested that the Examiner address each of Applicants' arguments or withdraw the rejections.

The Examiner indicated that the specification, while enabling a method for treating asthma using a particular CpG oligonucleotide (SEQ ID NO:10), did not enable a method of treating an allergic response or allergy related disorder using a CpG oligonucleotide with any size or formula. The Examiner further concluded that undue experimentation would be required for a skilled person in the pertinent art to make and use the claimed invention. In particular, the Examiner pointed out that the state of the art was unpredictable with regard to the use of CpG oligonucleotides in treating allergic disorders, and that the instant application failed to provide working examples.

Applicants respectfully request reconsideration for the reasons set forth below.

Claim 19, the only pending claim, is directed to a method for treating an allergic response to an antigen or allergy related disorder during antigen specific immunotherapy of a subject comprising administering to the subject a first composition comprising a 5'CpG3' immunostimulatory oligonucleotide and a second composition comprising an antigen. The CpG oligonucleotide can inhibit the allergic response in the subject and, together with the antigen, can modulate the immune response to the antigen.

The enablement requirement under 35 U.S.C §112 inquires whether the application, when filed, contained sufficient information to enable one skilled in the pertinent art to make and use the claimed invention commensurate in scope with the claims without undue experimentation. *See* MPEP 2164.01. Applicants herewith submit that the reasons proffered in the Office Action are not sufficient to support that undue experimentation is required for a skilled person in the art to make and use the claimed invention.

First, several papers were cited to support the lack of enablement rejection and, in particular, to support the argument that the state of the art is unpredictable with regard to the use of CpG oligonucleotides for treating allergy. Applicants respectfully traverse.

McCluskie et al., 1999 and Krieg et al., 2000 were cited for the proposition that biological responses to the administration of CpG containing oligonucleotides vary depending on the mode of administration and the organism.

Applicants have dropped the response to the rejection in view of McCluskie et al. in view of the Examiner's clarification on the record that the rejection was dropped.

Krieg et al. is a review article describing the uses of CpG oligonucleotides. Applicant cannot locate the teaching that "bioresponses to the administration of CpG vary depending on the

mode of administration and the organism" on page 524, to which the Office Action specifically pointed. In fact, Krieg et al. teaches that synthetic CpG oligonucleotides, by inducing Th1-biased immune responses, have shown significant effects as vaccine adjuvants and as immunotherapeutics for treatment of cancer and allergic conditions in model systems. *See* the Abstract. It further teaches that "the potent Th1 adjuvant effect of CpG DNA can even override preexisting Th2 immune responses; it has been used as an adjuvant for allergy vaccines, where it induces Th1 responses to antigens in the presence of a preexisting Th2 response, leading to decreased symptoms following subsequent allergen inhalation." *See* pg 524. In sum, the teaching of Krieg et al. does not cast doubt on the enablement of the claimed invention.

The Examiner has cited Wohlleben et al. 2000 to support the arguments that (1) "the state of the art questions whether 'CpG-ODNs' can be used in humans to inhibit the development of asthma, and that (2) "all approaches that induce Th1 responses have the potential side-effects of Th1 cell-mediated inflammation potentially causing serious tissue damage."

Applicants respectfully disagree with the Examiner's understanding of Wohlleben et al. In fact, Wohlleben et al. provides a favorable view of CpG oligonucleotides and their usefulness in treating asthma. The use of CpG oligonucleotides is identified in the abstract and conclusion of the paper as one of "the most promising approaches" for the treatment of atopic diseases and particularly asthma. Even the cited paragraph on page 620 relates to the expectation that CpG oligonucleotides will be effective in humans. For example, it teaches that the "results obtained from animal models suggest that it is *probable* that these approaches might also be successful in humans to reduce the development of atopic disorders." *See* pg 620, 2nd para. It further teaches that "[t]his suggests that the treatment of humans with CpG-ODNs could be very effective in inhibiting the development of asthma." *See* pg 620, Col. 2, 1st para. Taken together, the teachings found in Wohlleben et al. do not support the conclusion that the claimed invention was not enabled at the time the instant application was filed.

Further, the teachings of Wohlleben et al. with respect to potential harmful side effects do not support a lack of enablement of the pending claims. MPEP 2164.01(c) has made it clear that an applicant need not demonstrate that his invention is safe. Thus, whether a drug is safe or has no harmful side effects is not an appropriate test for enablement. In fact, one cannot possibly determine the parameters of safety without a controlled clinical trial. However, the law is well established that a clinical trial is not required for enablement. Additionally, Wohlleben et al.

does not provide sufficient evidence showing that CpG-ODNs would cause harmful side effects when applied in humans. To the contrary, on page 620 immediately following the discussion of side effects, Wohlleben et al. states that "it is totally unclear if this can also occur in healthy rodents or, more importantly, humans." *See* pg 620, Col. 2, 1st para.

Satoh et al. was also cited to demonstrate that CpG was associated with dangerous side effects. This reference is an abstract describing a study on the effects of CpG oligonucleotides administered subcutaneously to mice that are treated with DNFB. It was concluded that CpG oligonucleotides were responsible for worsening of the allergic contact dermatitis (ACD) induced by DNFB. As mentioned above with respect to Wohlleben et al, the issue of whether a drug is safe and has no side effects is not an appropriate test for enablement. Additionally, the teachings of the Satoh et al reference are not sufficient to establish a lack of enablement for the claimed invention. Note that the ACD is in fact caused by DNFB treatment. The fact that CpG oligonucleotides may contribute to type IV hypersensitivity responses initiated by DNFB does not establish that CpG oligonucleotides would cause ACD in the absence of DNFB.

The Examiner further cited Kline et al., 2002, and Kline et al., 1998 to demonstrate that in some instances, the use of CpG alone is ineffective for the treatment of asthma. In particular, the Examiner asserted that Kline et al., 2002, disclosed that "a single treatment of CpG-ODN alone was ineffective in reducing the manifestations consistent with asthma in this animal model." The section of the paper identified by the Examiner on page L172 relates to an experiment designed to model "persistent asthma in humans, who, by current standards of treatment, require intensive anti-inflammatory therapy." The claimed invention does not require that the persistent asthma be treated with a single dose of CpG. Doses are within the purview of those skilled in the art, and the data in Kline et al., 2002, supports that monotherapy at appropriate doses can work. As a matter of fact, many drugs, including those for treating chronic asthma, are not effective when used as a single dose. Therefore, the fact that a single dose of CpG is ineffective does not negate the conclusion that CpG ODN is a promising approach for treating asthma and allergy. Additionally, the claimed invention is directed to the use of a combination of CpG and antigen.

The Examiner has also indicated that Kline 2002 teaches that "splenocytes from OVA-treated mice did not develop an antigen specific Th1 phenotype. However, mice treated with CpG ODN and OVA had a marked shift toward a Th1 response to antigen as well as reduction in

airway eosinophila, serum IgE and bronchial hyperreactivity (p. L176, col. 2)." This statement does not support a lack of enablement of the claimed invention. The failure to develop a Th1 phenotype in mice in response to OVA treatment is not inconsistent with the invention. The second sentence is consistent with and even supportive of the utility of the invention.

Weiner is cited for the proposition that the molecular mechanism of CpG is unknown. However, knowledge of the mechanism of a claimed invention is not a prerequisite for its patentability. *See* Newman v. Quigg, 877 F.2d 1575, 1581. The instant application identifies consistent changes in the immune system at the cellular level in response to CpG administration. These immune responses are therapeutically relevant. Additionally, Table 1 of Weiner lists examples of cellular effects arising from immunostimulatory CpG ODN. A lack of understanding of the molecular mechanism does not render the cellular results unpredictable. Other statements in Weiner are consistent with enablement of the claimed invention. For instance, it teaches that "[s]tudies to date suggest CpG DNA could have significant therapeutic promise in the treatment of a variety of disorders, including infectious disease, allergy, and cancer." *See* pg 456, 1st column. In addition, page 457 under "In vivo effects of CpG ODN" shows that "extensive studies have been done in rodents, and some studies have been done in non-human primates. The observed *in vivo* data fits well with the *in vitro* data outlined above."

Agrawal et al has been cited in support of the assertion that the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable. In particular, the examiner has identified pages 78-80 as being particularly relevant. Agrawal et al is a review article describing antisense oligonucleotides. The authors suggest on page 78 that in order to *reduce* non-antisense related activity, it is best to avoid CpG motifs. The authors also indicate that if it is not possible to avoid CpG motifs, then it is possible to make modifications to reduce the CpG activity of the oligonucleotide. One of the suggested modifications is to replace the cytosine base of the CpG with a 5-methyl cytosine base. The instant specification, however, teaches that a CpG containing oligonucleotide has *an unmethylated C* in the CpG motif. Further, the cited section of Agrawal et al teaches that the proposed modifications "significantly reduced side effects". Thus, Agrawal et al does not teach that immune stimulation was abolished with any of these proposed modifications, just reduced.

The Examiner has also cited Dziadzio et al. to support the statement that the state of the art is "unpredictable with regard to the use of ISS-ODN in treating asthma." However,

Dziadzio et al. actually teaches that CpG containing oligonucleotides are encouraging as potential therapies for allergic disease. After summarizing several sets of data on page 280, Dziadzio et al teach:

> "These data suggest that ISS-ODN can induce a Th1 phenotype prior to allergen exposure. It appears that even without the presence of allergen, CpG motifs can induce a Th1 phenotype in multiple cell types including B cells, antigen-presenting cells (macrophages, dendritic cells), T cells, and NK cells. The expression of Th1 cytokines along with an upregulation of costimulatory molecules on these cells underscores the importance of ISS-ODN in Th1 and innate immune responses. The persistence of a Th1 response after antigen challenge in sensitized mice is encouraging as potential therapy for allergic disease." (page 280, 2nd-3rd full paragraphs).

The teachings of Dziadzio et al. as a whole do not support a finding that the claimed invention was unpredictable at the time of filing the instant application.

Metzger et al., 1999, is cited to show that "oligonucleotide therapy for asthma seems unlimited, but confirmation awaits the extension for animal models to human studies." This reference summarizes methods of oligonucleotide therapy of allergic asthma, including DNA vaccination with CpG DNA as a vaccine adjuvant. It teaches that "CpG DNA not only promotes nonspecific innate immunity but also generates antigen-specific immune responses" and that "[t]hey have been described to be actually more potent than Freund's adjuvant in producing TH1-like vaccine responses." *See* pg 264, col. 1. Thus, the teaching of Metzger as a whole, also does not support the finding that the claimed invention was unpredictable at the time of filing this application.

Although the Examiner did not specifically include Hussain et al, Van Uden et al and Kussebi in the list of references included for maintaining the lack of enablement rejection, Applicants have reiterated the arguments since the original rejection was included in the office action.

The Examiner has cited Hussain et al., 2004, to support the proposition that "combined data from our studies with the murine model of allergic rhinitis and limited data from skin favor the idea that CpG ODN may be an attractive therapy in the treatment of acute atopic dermatitis." This statement supports the enablement of the claimed invention.

The Examiner has cited Van Uden et al for the concept that each ISS has a minimum length limitation and that potential side effects associated with treatment must be considered. With respect to the section of the paper that refers to the length of ODN, the authors do not conclude that there is a specific rule for the length of the ODN. The authors hypothesize that different lengths and flanking sequences have an impact on the activity of the ODN. The patent application as filed confirms that certain motifs and lengths are preferred. However, it is believed that most unmethylated CpG containing oligonucleotide within the scope of the claims would have the ability to induce *in vivo* a pattern of cytokine release which would drive the immune system toward a Th1 response when administered in an appropriate dosage.

The examiner quotes some language from page 907 column 2 and page 908 column 1 related to the issue of side effects associated with CpG oligonucleotide administration. Again, as noted above, safety is beyond the standard of the enablement requirement. *See* MPEP 2164.01(c). In addition, each of these statements, however, is taken out of context. After the quoted section the authors point out that such side effects have not been observed. For example, the Examiner has pointed to the statement on page 907 that "[t]here is always the possibility of unwanted effects of the powerful immune stimulation that ISS delivers" and compared the effects of CpG with LPS. In contrast to the implications from the language quoted in the office action, immediately following that paragraph the authors conclude

> "Although these reports demonstrate the possibility of shock in extreme cases of sensitization or concurrent LPS exposure, there has never been a reported case of ISS alone causing shock in any kind of healthy animal at any dose." (Page 908 column 1 lines 2-6) and
> "We and others have never observed gross inflammation in response to ISS in ODN or plasmid form in any experimental animals or humans." (page 908 first column first full paragraph)

The Examiner has also stated that Van Uden et al teaches that "ISS could cause excessive local inflammation as seen with other powerful Th1 adjuvants, such as CFA." In contrast to this statement, the authors point out an experiment in which bacterial DNA complexed with CFA is injected into mice. It is concluded that

> "When the mixture is given to preautoimmune NZB/NZW F1 mice, they develop antibodies that cross-react with mammalian DNA, but surprisingly they are actually protected from their spontaneous autoimmune disease. There

> still are no examples of ISS directly causing any type of autoimmune disease in animal models." (page 908 paragraph bridging columns 1 and 2).

Accordingly, Van Uden et al. does not provide sufficient evidence showing that CpG ODN is unsafe when applied in humans.

The Examiner has cited Kussebi to show that "in general, the direct conjugation of CpG-ODNs to allergenic proteins or peptides was more effective than their co-administration, possibly because of enhanced interaction with dendritic cells via the CpG moiety (p. 300, col. 1)." The claims are not limited by whether the ODN and antigen are conjugated. Thus, the claims encompass administration of ODN and antigen, whether conjugated or not. Additionally, the above statement does not deny CpG's effects of inducing immune responses when co-administered with allergenic proteins. To be patentable, an invention need not be superior than any known relevant technology. *See* Custom Accessories v. Jeffrey-Allan Indus., 807 F.2d 955, 960 (Fed. Cir. 1986) ("Finding that an invention is an "improvement" is not a prerequisite to patentability. It is possible for an invention to be less effective than existing devices but nevertheless meet the statutory criteria for patentability.")

Overall, the references cited by the Examiner are not sufficient to support the conclusion that the state of the art is unpredictable with regard to the use of CpG oligonucleotide in treating allergic disorders. To the contrary, these references provide numerous *in vitro* and *in vivo* data demonstrating that administration of CpG-ODNs is a promising approach to stimulate a Th1 response in the recipient and thus to treat diseases such as asthma and allergy.

Second, the Examiner stated that the specification, disclosing the use of a particular CpG oligonucleotide (SEQ ID NO:10) to treat asthma in a murine model, did not provide sufficient enablement for the claimed method – treating allergy by administering to a subject an immunostimulatory CpG oligonucleotide of any size and an antigen. Applicant respectfully disagrees.

The specification of the instant application has disclosed a class of oligonucleotides having a common motif, a CpG dinucleotide, that can produce a Th1 biased immune response. In particular, the CpG oligonucleotides can induce monocytic cells and other immune cells to produce Th1 cytokines, including IL-12, IFN-γ and GM-CSF. *See* pg 7, lines 15-17. To support this statement, the application has provided numerous data obtained both *in vivo* and *in vitro*,

using an adequate number of different CpG-containing oligonucleotides (more than 40 oligonucleotides were tested). *See e.g.*, pg 20, Table 1, pg 21, Table 2 and pg 23, Table 3.

The data in the application, including that represented in Tables 1-3 establishes that the unmethylated CpG oligonucleotide is capable of inducing immune responses. The data in Table 5 demonstrates that the immune responses has the characteristic pattern of Th1 response. *See* pg 27. Eleven different oligonucleotides induced a Th1 cytokine profile, demonstrating that CpG oligonucleotides can consistently drive the immune system toward a Th1 response. Pursuant to the data presented in the application, a skilled artisan would have recognized that many oligonucleotides containing the unmethylated CpG motif would be capable of invoking a Th1 immune response in a subject. In other words, the instant application is not limited to a particular CpG oligonucleotide, such as SEQ ID NO:10.

Pursuant to Chiron Corp. v. Genetech, Inc., 363 F.3d 1247, Applicant is not required to provide an example of using a CpG oligonucleotide of any size and formula to treat allergy, for the artisan's knowledge of prior art and routine experimentation can often fill gaps interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments.

Allergy is mediated by a Th2 immune response and a Th1 immune response is protective against allergy. *See* specification pg 41, lines 15-35. Thus a skilled person in the art would have acknowledged that redirecting a Th2 response to a Th1 response in a subject would be effective in treating or preventing allergy. In view of the above disclosure that CpG oligonucleotides are capable of invoking a Th1 response, it is predictable that CpG oligonucleotides, as recited in claim 19, can be used to treat and prevent allergy. In addition, the references cited by the Examiner also have demonstrated the promising effects of CpG oligonucleotides in treating allergy. The claimed invention is enabled because knowledge of the state of the art would allow one skilled in the art to extrapolate how to make and use the claimed invention from the disclosure of the instant application.

The Examiner also indicated that "the amount of direction or guidance presented in the specification and the presence or absence of working example is a hindrance to practicing the claimed invention." Specifically, the Examiner pointed out that "the quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations of the CpG to target appropriate cells and/or tissues in any and/or all organisms, and further whereby treatment

effects are provided for the claimed conditions." *Id*, pgs 9-10. Further, the Examiner stated that there was no working example provided in the instant application.

Applicant respectfully disagrees. As noted above, Applicant is not required to provide each and every piece as to how to make and use the claimed invention, for the gaps can be filled by the knowledge of a skilled person in the art or routine experimentation. *See* Chiron Corp. v. Genetech, Inc., 363 F.3d 1247. The aforementioned prior art references have consistently supported the use of CpG to invoke a Th1 response both *in vitro* and in animal models, a common mechanism of action that contributes to the therapeutic effects of CpG oligonucleotides. These references have also demonstrated the promising therapeutic effect of immunostimulatory CpG oligonucleotides in treating diseases such as asthma and allergy. Moreover, data presented in the specification, including the use of a CpG oligonucleotide for the treatment of allergic asthma in a murine model, also teaches how to make and use the claimed invention. In light of the prior art, as well as the disclosure of the instant application, one skilled person in the pertinent art would have known how to administer CpG-ODNs to a subject to treat allergic disorders by stimulating a Th1 immune response via routine experimentation. Thus the enablement requirement under 35 U.S.C. § 112 has been satisfied. *See* In re Johnson, 282 F.2d 370, 373.

Further, actual reduction to practice prior to filing is not required to satisfy the enablement requirement. *See* Gould v. Quigg, 822, F.2d 1074, 1078. MPEP 2164.02 also makes it clear that lack of working example or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the ground of lack of enablement. Accordingly, lack of a working example of the claimed invention should not be a per se bar to patentability for lack of enablement.

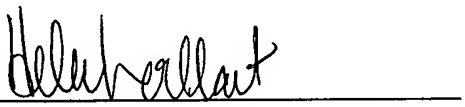
In view of the foregoing, the office action does not provide persuasive reasons that a skilled person in the art would need undue experimentation to make and use the claimed invention. Thus, withdrawal of the rejection of claim 19 under 35 U.S.C. §112 is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Arthur M. Krieg et al., Applicant(s)

By: 

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